PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the Application of:

Philippe CROS et al.

Application No.: 08/945,731

Filed: November 10, 1997 Docket No.: WPB 40330

For: NUCLEIC ACID ISOLATION

#12
BJ
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BRIEF ON APPEAL

Appeal from Group 1600

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APPENDIX A-1

I. INTRODUCTION

This is an Appeal from a Final Rejection mailed April 8, 1999, finally rejecting claims 1-22 of the above-identified application. No claims are allowed.

A. Real Party in Interest

The real party in interest for this Appeal and the present application is Bio Merieux, by way of an Assignment recorded in the U.S. Patent and Trademark Office starting at Reel 8890, Frame 0988.

B. Statement of Related Appeals and Interferences

There are presently no appeals or interferences, known to Appellants, Appellants' representatives or the Assignee, which will directly affect or be directly affected by or have a bearing upon the Board's decision in the pending Appeal.

C. Status of Claims

Claims 1-3 and 5-23 are pending. Claims 1-3 and 5-23 stand rejected and are on appeal. All of claims 1-3 and 5-23 are set forth in the attached Appendix. Claims 1 and 3 are independent. Claims 2, 5-16, 18-21 and 23 ultimately depend from claim 1; and claims 17 and 22 ultimately depend from claim 3.

D. Status of Amendments

An Amendment After Final Rejection is being filed herewith. Since the Amendment merely cancels claim 4; corrects obvious errors in each of claims 1, 3, 5 and 10; and adds new claim 23 directed to the subject matter deleted from claim 5, it should be entered pursuant to 37 C.F.R. §1.116. Therefore, throughout the Appeal Brief, including in the Appendix, it has been assumed that the Amendment After Final Rejection has been entered.

II. THE INVENTION

The present invention is directed to a process for the selective isolation of nucleic material present in a sample by adsorption of the nucleic material onto a particulate support

comprising a functionalized, particulate polymer having a lower critical solubility temperature (LCST) that is between 25 and 45°C. Page 2, lines 5-7, and page 3, lines 18-37. The polymer comprises: (a) a first water-soluble monomer of an acrylamide or an acrylamide derivative; (b) a cross-linking agent; and (c) a second cationic and water-soluble functional monomer. Page 2, lines 21-25. In the process, the sample is brought into contact with an adsorption reagent comprising a discontinuous phase of the particulate support in an aqueous continuous phase to adsorb the nucleic material onto the particulate support. Page 2, lines 17-32.

In the contacting step, the reaction medium has a pH at most equal to 7, an ionic strength at most equal to 10^{-2}M, and a temperature less than the LCST of the polymer. Page 2, line 33, to page 3, line 2. As demonstrated in Example 2 of the present application, in addition to temperature, the pH and the ionic strength of the reaction medium have a significant effect on the ability of the nucleic material to be adsorbed by the polymer material. Page 15, line 16, to page 17, line 15. In particular, at acidic pH, the polymer particles, which contain cationic monomers, are widely positively charged. As a result, the negatively charged nucleic acids attach to the particles via electrostatic forces. Page 16, lines 29-31, and Figure 2. In addition, as demonstrated in Figure 4, the attractive electrostatic forces between the negatively charged nucleic material and the positively charged polymer surface decreases with the increase in ionic strength. As a result, there is a decrease in the attachment of the nucleic material to the polymer with an increase in ionic strength. Page 17, lines 3-7.

III. THE APPLIED REFERENCES

The applied references are:

1) European Patent Application No. 0 161 881 by Itoh et al. (hereinafter "Itoh");

2) U.S. Patent No. 4,912,032 to Hoffman et al. (hereinafter "Hoffman");

3) U.S. Patent No. 5,122,600 to Kawaguchi et al. (hereinafter "Kawaguchi"); and

4) U.S. Patent No. 5,508,164 to Kausch et al. (hereinafter "Kausch").

IV. ISSUE

The only issue on appeal is whether claims 1-3 and 5-23 would have been obvious to one of ordinary skill in the art under 35 U.S.C. §103 over the combination of Itoh, Hoffman, Kawaguchi and Kausch.

V. GROUPING OF CLAIMS

Each claim of this patent application is separately patentable, and upon issuance of a patent will be entitled to a separate presumption of validity under 35 U.S.C. §282. For convenience in handling of this Appeal, the claims will be argued in eight Groups as follows:

Group I: claims 3, 17 and 22;

Group II: claims 1, 2, 11-16 and 18-21;

Group III: claims 5 and 23;

Group IV: claim 6;

Group V: claim 7;

Group VI: claim 8;

Group VII: claim 9; and

Group VIII: claim 10.

Thus, pursuant to 37 C.F.R. §1.192(c)(7), in this Appeal, the rejected claims within each Group will stand or fall together. However, the rejected claims of each Group do not stand or fall together with the rejected claims of any other Group.

VI. ARGUMENT

Claims 1-3 and 5-23 are rejected under 35 U.S.C. §103 as having been obvious over the combination of Itoh, Hoffman, Kawaguchi and Kausch. However, the combination of these references would not have rendered obvious the claimed invention to one of ordinary skill in the

art. In particular, the cited reference, considered alone or in combination, do not teach or suggest the claimed processes.

A. Factual Inquiries to Determine Obviousness/Non-Obviousness

Several basic factual inquiries must be made in order to determine obviousness or non-obviousness of claims of the patent application under 35 U.S.C. §103. These factual inquiries are set forth in Graham v. John Deere Co., 383 U.S. 1, 17, 148 USPQ 459, 467 (1966):

> Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or non-obviousness of the subject matter is determined.

The specific factual inquiry set forth in Graham have not been considered or properly applied by the Examiner in formulating the rejection of the subject claims. Particularly, the scope and content of the prior art and the level of ordinary skill in the pertinent art were not properly determined, demonstrated and applied to the claimed invention.

In the present case, proper consideration of the factual inquiries demonstrate non-obviousness of the claimed invention. In particular, the cited references do not teach or suggest the claimed processes.

B. The Cited References Do Not Teach or Suggest the Subject Matter of Group I

Claim 3 of Group I recites a process for the isolation in aqueous phase of a nucleic material present in a sample by adsorption of the nucleic material onto a particulate support. The method comprises: (a) providing an adsorption reagent comprising a sol consisting of an aqueous continuous phase and a discontinuous phase of the particulate support; (b) bringing into contact the adsorption reagent with the sample containing the nucleic material to adsorb the nucleic material to the particulate support, wherein the reaction medium has an ionic strength at most equal to 10^{-2}M, a pH at most equal to 7, and a temperature less than the LCST of the polymer; (c) optionally observing that the adsorption has taken place; and (d) separating the

discontinuous phase from the continuous phase. In the process, the particulate support comprises a functionalized, particulate polymer, the polymer being obtained by polymerization of (1) a first water-soluble monomer of an acrylamide or of an acrylamide derivative, (2) at least one cross-linking agent, and (3) at least a second cationic and water-soluble functional monomer, the polymer having a predetermined LCST between 25 and 45°C. Claims 17 and 22 of Group I ultimately depend from claim 3 of Group I.

1. Itoh Does Not Teach or Suggest the Subject Matter of Group I

Itoh is directed to a high molecular composite material having, as one component thereof, a homopolymer or copolymer of an N-substituted derivative of an acrylamide or methacrylamide. Page 1, lines 2-6. Itoh teaches that the polymeric material permits the formation of composite materials with a very large number of low molecular or high molecular compounds. Page 4, lines 7-10. Among such compounds, Itoh teaches compounds containing active hydrogen and compounds containing hydrophobic groups. Page 19, lines 17-20. Itoh then goes on to list various compounds that can be attached to the polymer from page 19, line 23, to page 32, line 14. Included in Itoh, at page 45, lines 3-4, is a passing reference to nucleic acids as being an example of a compound substituted by groups containing active hydrogen atoms. However, Itoh does not teach appropriate conditions at which nucleic acids can be attached to the polymer.

a. Itoh Does Not Teach or Suggest Using a Temperature Less Than the LCST of the Polymer to Adsorb Nucleic Material

Itoh teaches at least two distinct methods for holding and releasing the various compounds to and from the polymer. With regard to compounds substituted by groups containing active hydrogen atoms, such as nucleic acids, Itoh teaches that the compounds develop intermolecular forces such as hydrogen bonds, hydrophobic bonds or the like with the homopolymers or copolymers. Page 44, lines 22-25. Itoh teaches that "[t]hese compounds may

be held at high temperatures and released at low temperatures." Page 45, lines 11-13. This teaching suggests the use of higher temperatures for holding nucleic acids, thus teaching away from temperatures less than the LCST of the polymer, as recited in the present claims.

In a totally separate technique for holding components to the polymer, Itoh teaches utilizing the property of the homopolymers or copolymers taught therein to absorb and hold water upon contact with aqueous solutions but, when heated, shrink and release water. Page 44, lines 3-6. In this technique, the homopolymers or copolymers may be heated to release the components, which must be low molecular weight compounds. Page 46, lines 4-8. In addition, the shrink and swell property of the polymer can also be utilized in a technique in which the low molecular compounds are held at high temperatures and released at low temperatures. Page 47, lines 16-18. However, Itoh makes no mention of utilizing the shrink and swell properties of the polymers to hold nucleic acids to the polymer.

The Final Rejection states that high molecular weight substances are retained at low temperatures and released at high temperatures. Although Itoh teaches that, when the material is "held in gel-like polymers, they are held at low temperatures as the gel-like polymers are swollen at low temperatures and are released at high temperatures as the gel-like polymers are shrunk at high temperatures," Itoh does not indicate that this section relates to high molecular weight compounds. Page 47, lines 19-24. Although the preceding paragraph relates to low molecular weight compounds, what determines the influence of temperature is not the molecular weight of the compounds to be held. Instead, the influence of temperature depends on "how the holding and release takes place." Page 47, lines 6-8. Thus, Itoh teaches that, when the release of the low molecular weight compounds takes place as a result of diffusion, in contrast to the case where the materials are held in gel-like polymers, the low molecular weight compounds are held at high temperatures and released at low temperatures. Page 47, lines 6-18. However, Itoh does

not state that, when the release of the compound is based on diffusion, the opposite result is obtained with high molecular weight compounds. Instead, Itoh merely suggests that only low molecular weight compounds can be held by the shrink and swell of the polymers. Page 45, lines 14-18. Thus, Itoh clearly does not teach or suggest whether nucleic acids can be held based on the shrink and swell of the polymers, much less whether they are held at high temperatures and released at low temperatures or held at low temperatures and released at high temperatures based on the shrink and swell of the polymer. As a result, Itoh does not teach or suggest utilizing temperatures less than the LCST of the polymer to hold nucleic acids to the polymer by its shrink and swell property.

The Advisory Action states, in section 6, that the above-mentioned recitation, at page 45, lines 11-13, of holding compounds at high temperatures and releasing them at low temperatures is referring to "the entrapment of high molecular weight molecules by the shrinking and swelling of the pores of the gel, and does not refer to the adsorption of molecules to the gel by ionic or electrostatic forces." Appellants respectfully disagree. The paragraph indicates that there are different techniques for holding and releasing valuable substances depending on the valuable substance. Page 44, lines 16-18. The paragraph then goes on to discuss "compounds substituted by groups containing active hydrogen atoms." Page 44, lines 18-19 (emphasis added). Included among the list of compounds containing active hydrogen atoms is the only reference to nucleic acids in Itoh. Page 45, lines 3-4. The paragraph states that these compounds "can develop intermolecular forces such as hydrogen bonds, hydrophobic bonds or the like with the homopolymer or copolymers." Page 44, lines 23-25 (emphasis added). Thus, it is clear that this paragraph is directed to the first method discussed above for holding and releasing the various compounds in which the compounds are held based on intermolecular forces provided by active hydrogen atoms, not the second method in which the compounds are held based on the swell and

shrink of the polymer. Therefore, the statement on page 45, lines 11-13, that "[t]hese compounds may be held at high temperatures and released at low temperatures" is clearly directed to compounds containing active hydrogen atoms, such as nucleic acids, which are held by intermolecular forces, not to compounds held by the shrink and swell of the polymer, which as discussed above can be held at high temperatures and released at low temperatures or held at low temperatures and released at high temperatures depending on how the holding and release take place. In addition, since this paragraph makes the only reference to nucleic acids, Itoh only teaches the use of high temperatures to hold nucleic acids, thus teaching away from the claimed invention, which recites the use of temperatures below the LCST of the polymer to adsorb the nucleic material to the polymer.

b. Itoh Does Not Teach or Suggest Cross-linked Polymers Containing Cationic Monomers

As discussed above, Itoh is directed to a high molecular composite material having, as one component thereof, a homopolymer or copolymer of an N-substituted derivative of an acrylamide or methacrylamide. As a co-monomer, Itoh teaches hydrophilic monomers, ionic monomers and hydrophobic monomers. Page 7, lines 4-7. Examples of ionic monomers provided in Itoh include acids and amines. Page 7, lines 19-24. Itoh teaches eight potential methods to insolubilize the polymer. Included among these eight techniques is the use of a cross-linkable monomer. Page 13, line 25 to page 14, line 5. However, Itoh provides no motivation to select a cross-linked polymer containing ionic monomers, much less containing cationic monomers, from the large group of homopolymers and copolymers taught therein.

The Advisory Action states, in section 4, that Itoh teaches the use of cationic monomers in cross-linked polymers at page 24, lines 11-21. However, this section of Itoh makes no reference to cross-linked polymers. Although Appellants agree that Itoh makes reference to the use of ionic co-monomers and separately makes reference to cross-linked polymers, Appellants

do not agree that Itoh provides any motivation to select a cross-linked polymer containing cationic monomers to isolate nucleic material according to the present invention. In particular, Itoh teaches a wide variety of copolymers for a wide variety of processes. It does not teach the type of polymer that would be appropriate for the process of the present invention.

c. Itoh Does Not Teach or Suggest a pH At Most Equal to 7 or an Ionic Strength At Most Equal to 10^{-2}M

Itoh does not teach or suggest appropriate pH and/or ionic strength conditions for holding nucleic acids to the polymers of the present invention, which contain cationic monomers. As demonstrated in Example 2 of the present application, these forces have a significant affect on whether the polymer is able to hold the nucleic material. Although Itoh teaches that there may be a relationship between the pH of the system and whether the components are held to or released by the polymer, Itoh does not teach or suggest how the various techniques for holding various components to the polymer are affected by changes in the pH. In particular, Itoh does not teach or suggest how pH affects the ability of the polymer to hold nucleic acids. In addition, Itoh does not teach or suggest how pH will affect the ability of polymers containing cationic monomers to hold nucleic acids at temperatures below the LCST of the polymer.

The Advisory Action states, in section 7, that Itoh teaches the use of acidic pH at page 48, line 25, to page 49, line 9, and at page 49, lines 18-19. However, these sections of Itoh are directed to techniques for holding ampholytic electrolytes such as amino acids or proteins. Page 49, lines 1-2. Itoh does not provide any teaching or suggestion of acidic pH to isolate nucleic material.

d. Conclusion

The claimed invention is directed to the use of a particular reaction medium and the use of a particular polymer in order to isolate nucleic material from a sample. Itoh does not provide any motivation to select the particular features recited in the claimed invention in order to isolate

nucleic material. In particular, Itoh does not teach or suggest selecting a pH at most equal to 7, an ionic strength at most equal to 10^{-2} M, and a temperature less than the LCST of the polymer, as well as the use of a cationic monomer in a cross-linked polymer, to isolate nucleic material from an aqueous phase.

2. Hoffman Does Not Teach or Suggest the Subject Matter of Group I

Hoffman is directed to methods for delivering substances into, removing substances from, or reacting substances with a selected environment utilizing polymer gels or coatings exhibiting either an upper or lower critical solution temperature. Col. 1, lines 16-22. As polymers having an LCST, Hoffman teaches substantially hydrophobic polymers of N-substituted acrylamides or methacrylamides, hydroxy alkyl cellulose, polyoxazolidone, polyvinylmethylether, polyethylene oxide, polymethacrylic acid, or copolymers thereof. Col. 4, lines 31-38. Hoffman does not teach or suggest a copolymer of an acrylamide or acrylamide derivative monomer with a cationic functional monomer or a cross-linked polymer.

To bind a component that is part of an affinity binding pair, such as DNA or RNA, Hoffman teaches physically or chemically binding the other binding component, namely, complementary DNA or RNA, to the polymer. The polymer gel/binding component is then contacted with a solution containing the second component of the binding pair. The mixture is then incubated at a temperature sufficient to cause the polymer gel to absorb liquid from the solution containing the second binding component, thereby allowing the second binding component to specifically bind to the first binding component. Col. 4, line 57, to col. 5, line 19. Hoffman does not teach or suggest relying merely on the absorption of the DNA or RNA to the polymer to remove the DNA or RNA from the sample.

In addition, Hoffman provides no teaching or suggestion of using a pH at most equal to 7 and an ionic strength at most equal to 10^{-2} M. Although Hoffman teaches that buffer salts

surrounding the solution make it easier to deliver methylene blue on heating above the LCST at column 15, lines 53-56, Hoffman provides no teaching or suggestion as to how the above-mentioned method for holding DNA or RNA to its binding pair on the polymer would be affected by a pH at most equal to 7 and an ionic strength at most equal to 10^{-2}M. Therefore, one of ordinary skill in the art would not have been motivated by the teachings of Hoffman to select a reaction medium in which the pH is at most equal to 7 and the ionic strength is at most equal to 10^{-2}M.

3. Any Proper Combination of Itoh and Hoffman Would Not Teach or Suggest the Present Method

Hoffman is directed to techniques for holding substances to a polymer gel by the swell and shrink property of the gel. Thus, assuming any combination with Itoh is proper, Hoffman can only be properly combined with the teachings of Itoh directed to holding substances to the gel based on the shrink and swell properties of the gel. At least these teaching of Itoh do not provide any motivation to select a pH at most equal to 7. In addition, Itoh does not provide any motivation to select a cross-linked polymer containing a cationic comonomer or an ionic strength at most equal to 10^{-2}M. Therefore, Itoh does not overcome the deficiencies of Hoffman.

4. Kawaguchi Does Not Overcome the Deficiencies of Itoh and/or Hoffman

Kawaguchi is directed to a DNA-immobilized microsphere comprising DNA chains having base sequences that bind to a specific protein. In Kawaguchi, the immobilization of DNA chains on the surface of the particles is obtained by a covalent bonding method. Col. 4, lines 66-68. Kawaguchi teaches the use of a buffer solution having a high salt concentration to release the proteins from the DNA. Col. 5, lines 51-54. However, the ionic strength at which proteins bind to and are released from DNA provides no indication of appropriate ionic strengths for holding nucleic material to the polymer. Thus, Kawaguchi does not overcome the deficiencies of Itoh and/or Hoffman.

5. Kausch Does Not Overcome the Deficiencies of Itoh and/or Hoffman

Kausch is directed to a method for the isolation and sorting of biological materials comprising anchoring the biological material to a support to immobilize it, labeling the biological material with a binding composition that is capable of binding to it, the composition also being attached to magnetic particles, and isolating individual components of the biological material by reversal of the immobilization step and exposure to a magnetic field. The Final Rejection states that the binding reaction took place in low ionic strength buffers and the release was effected with high ionic strength buffers. Upon review of Kausch, however, in particular columns 3-10 noted in the Final Rejection, although it appears that Kausch teaches the use of high salt concentrations to remove the binding composition and the magnetic particles from the biological material, Kausch does not teach or suggest that high salt concentrations can be used to remove the biological material from the support, much less from the polymers of the present invention. Therefore, Kausch does not overcome the deficiencies of Itoh and/or Hoffman.

6. Conclusion

Itoh does not teach or suggest the subject matter of Group I. None of Hoffman, Kawaguchi or Kausch can properly be combined with Itoh in a way in which they overcome the deficiencies of Itoh. Therefore, with regard to the subject matter of Group I, the rejection under 35 U.S.C. §103 should be withdrawn.

C. The Cited References Do Not Teach or Suggest the Subject Matter of Group II

Claim 1 of Group II is directed to a process for the isolation in aqueous phase of a nucleic material present in a sample by adsorption of the nucleic material onto a particulate support. Claim 1 of Group II includes all of the features of claim 3 of Group I. In addition, claim 1 includes a further step (e) in which the nucleic material is dissociated by desorption from

the particulate support by increasing the ionic strength up to an ionic strength greater than 10^{-2}M. Claims 2, 11-16 and 18-21 of Group II ultimately depend from claim 1 of Group II.

Because claim 1 of Group II includes all of the features of claim 3 of Group I, claim 1 is patentable over the combination of Itoh, Hoffman, Kawaguchi and Kausch for at least the reasons discussed in part B above. In addition, none of the applied references teach or suggest dissociating the nucleic material from the particulate support by increasing the ionic strength up to an ionic strength greater than 10^{-2}M. Although Hoffman teaches that buffer salts surrounding the solution make it easier to deliver methylene blue on heating above the LCST at column 15, lines 53-56, Hoffman provides no teaching or suggestion as to how the method for holding DNA or RNA to its binding pair on the polymer would be affected by an ionic strength greater than 10^{-2}M. In addition, although Kawaguchi teaches the use of a buffer solution having a high salt concentration to release the proteins from the DNA, the ionic strength at which proteins bind to and are released from DNA provides no indication of appropriate ionic strengths for releasing nucleic material from the polymer. Furthermore, although it appears that Kausch teaches the use of high salt concentrations to remove the binding composition and the magnetic particles from the biological material, Kausch does not teach or suggest that high salt concentrations can be used to remove the biological material from the support, much less from the polymers of the present invention. Therefore, with regard to the subject matter of Group II, the rejection under 35 U.S.C. §103 should be withdrawn.

D. The Cited References Do Not Teach or Suggest the Subject Matter of Group III

Claim 5 of Group III depends from claim 1 of Group II. In addition, claim 5 recites that the particulate support consists of a functionalized particulate polymer obtained by polymerization of (1) a first water-soluble monomer of acrylamide or of an acrylamide derivative, (2) at least one water-soluble cross-linking agent, and (3) at least a second cationic

and water-soluble functional monomer, the polymer having a predetermined LCST between 25 and 45°C. Claim 23 of Group III depends from claim 5 of Group III.

Because claim 5 of Group III depends from claim 1 of Group II, claim 5 is patentable over the combination of Itoh, Hoffman, Kawaguchi and Kausch for at least the reasons discussed in part C above. In addition, none of the applied references teach or suggest a process for isolating a nucleic material in an aqueous phase using an adsorption reagent comprising a sol consisting of an aqueous continuous phase and a discontinuous phase of the particulate support, wherein the particulate support consists of a functionalized, particulate polymer as recited in claim 5. In particular, to bind a component that is part of an affinity binding pair, such as DNA or RNA, Hoffman teaches physically or chemically binding the other binding component, namely, complementary DNA or RNA, to the polymer. Col. 4, line 57, to col. 5, line 19. Thus, the particulate support in Hoffman comprises a binding component, as well as the functionalized particulate polymer. As a result, the particulate support does not consist of the functionalized, particulate polymer of claim 5. Because Hoffman is directed to techniques for holding substances to a polymer gel by the swell and shrink property of the gel, assuming any combination with Itoh is proper, Hoffman can only be properly combined with the teachings of Itoh directed to holding substances to the gel based on the shrink and swell properties of the gel. Itoh does not teach or suggest holding nucleic material to a particulate polymer, either directly or indirectly, based on the shrink and swell property of the gel. Thus, Itoh does not provide any motivation to modify the process recited in Hoffman to exclude the complementary DNA or RNA. Therefore, with regard to the subject matter of Group III, the rejection under 35 U.S.C. §103 should be withdrawn.

E. The Cited References Do Not Teach or Suggest the Subject Matter of Group IV

Claim 6 of Group IV depends from claim 1 of Group II. In addition, claim 6 recites that the particulate support further comprises an organic or inorganic core, completely or partially coated with the particulate polymer, the core not modifying the adsorption properties of the polymer in relation to the nucleic material.

Because claim 6 of Group IV depends from claim 1 of Group II, claim 6 is patentable over the combination of Itoh, Hoffman, Kawaguchi and Kausch for at least the reasons discussed in part C above. In addition, none of the applied references teach or suggest a particulate support comprising, in addition to the polymer, an organic or inorganic core, completely or partially coated with the particulate polymer, the core not modifying the adsorption properties of the polymer in relation to the nucleic material. Therefore, with regard to the subject matter of Group IV, the rejection under 35 U.S.C. §103 should be withdrawn.

F. The Cited References Do Not Teach or Suggest the Subject Matter of Group V

Claim 7 of Group V depends from claim 6 of Group IV. In addition, claim 7 recites that the core is a polystyrene core.

Because claim 7 of Group V depends from claim 6 of Group IV, claim 7 is patentable over the combination of Itoh, Hoffman, Kawaguchi and Kausch for at least the reasons discussed in part E above. In addition, none of the applied references teach or suggest that the particulate support comprises a polystyrene core. Therefore, with regard to the subject matter of Group V, the rejection under 35 U.S.C. §103 should be withdrawn.

G. The Cited References Do Not Teach or Suggest the Subject Matter of Group VI

Claim 8 of Group VI depends from claim 6 of Group IV. In addition, claim 8 recites that the core comprises a magnetic compound.

Because claim 8 of Group VI depends from claim 6 of Group IV, claim 8 is patentable over the combination of Itoh, Hoffman, Kawaguchi and Kausch for at least the reasons discussed in part E above. In addition, none of the applied references teach or suggest a particulate support comprising a magnetic compound as its core. In particular, although Kausch teaches that the biological material-binding composition that is immobilized on a support may also be attached to magnetic particles, Kausch does not teach or suggest that the support comprises a magnetic compound at its core. Col. 5, lines 10-20. Therefore, with regard to the subject matter of Group VI, the rejection under 35 U.S.C. §103 should be withdrawn.

H. The Cited References Do Not Teach or Suggest the Subject Matter of Group VII

Claim 9 of Group VII depends from claim 1 of Group II. In addition, claim 9 recites that at least one probe and/or primer capable of specifically hybridizing to the nucleic material is added to the sample before contacting the adsorption reagent and the sample or is added to the reaction medium after contacting the adsorption reagent and the sample.

Because claim 9 of Group VII depends from claim 1 of Group II, claim 9 is patentable over the combination of Itoh, Hoffman, Kawaguchi and Kausch for at least the reasons discussed in part C above. In addition, none of the applied references teach or suggest a process wherein at least one probe and/or primer capable of specifically hybridizing to the nucleic material is added to the sample before contacting the adsorption reagent and the sample or is added to the reaction medium after contacting the adsorption reagent and the sample. Therefore, with regard to the subject matter of Group VII, the rejection under 35 U.S.C. §103 should be withdrawn.

I. The Cited References Do Not Teach or Suggest the Subject Matter of Group VIII

Claim 10 of Group VIII depends from claim 1 of Group II. In addition, claim 10 recites that the nucleic material is a primer and that after the adsorption reagent is brought into contact with the primer in order to obtain a hybridization reagent, and after the hybridization reagent has

been separated from the reaction medium, the hybridization reagent is brought into contact with a medium containing at least one nucleic acid or nucleic acid fragment under suitable conditions for the hybridization or the extension of the primer.

Because claim 10 of Group VIII depends from claim 1 of Group II, claim 10 is patentable over the combination of Itoh, Hoffman, Kawaguchi and Kausch for at least the reasons discussed in part C above. In addition, none of the applied references teach or suggest a process in which a hybridization reagent comprising the adsorption reagent and the nucleic material, which a primer, is brought into contact with a medium containing at least one nucleic acid or nucleic acid fragment under suitable conditions for the hybridization or the extension of the primer. Therefore, with regard to the subject matter of Group VIII, the rejection under 35 U.S.C. §103 should be withdrawn.

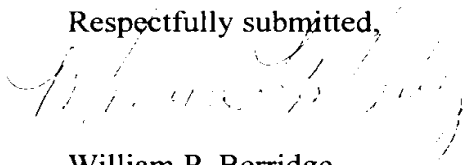
J. Summary

The applied references do not teach or suggest the processes of the present claims. In particular, Itoh does not teach or suggest a process for isolating nucleic material in which the nucleic material is adsorbed to a particulate support comprising a cross-linked polymer containing cationic monomers under conditions at which the pH is at most equal to 7, the ionic strength is at most equal to 10^{-2}M, and the temperature is less than the LCST of the polymer of the particulate support. In addition, none of Hoffman, Kawaguchi or Kausch can be properly combined with Itoh in order to overcome the deficiencies thereof. Accordingly, the claimed invention would not have been obvious to one of ordinary skill in the art at the time the present invention was made. The rejection should be reversed.

VII. CONCLUSION

For all the reasons discussed above, it is respectfully submitted that claims 1-3 and 5-23 define patentable subject matter under 35 U.S.C. §103. Therefore, Appellants respectfully request this honorable Board to reverse the rejection of claims 1-3 and 5-23.

Respectfully submitted,



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Attachment:
Appendix

APPENDIX

CLAIMS:

1. Process for the isolation in aqueous phase of a nucleic material present in a sample by adsorption of said nucleic material onto a particulate support, comprising:

(a) providing an adsorption reagent comprising a sol consisting of an aqueous continuous phase and a discontinuous phase of the particulate support, which comprises a functionalized, particulate polymer, said polymer being obtained by polymerization of (1) a first water-soluble monomer of acrylamide or of an acrylamide derivative, (2) at least one cross-linking agent, and (3) at least a second cationic and water-soluble functional monomer, said polymer having a predetermined lower critical solubility temperature (LCST) which is between 25 and 45°C,

(b) bringing into contact the adsorption reagent with the sample containing the nucleic material to adsorb the nucleic material to the particulate support,

wherein, in said contacting step (b), the reaction medium has:

- a pH at most equal to 7,

- an ionic strength at most equal to 10^{-2} M, and

- a temperature less than the LCST of the polymer,

(c) optionally observing that the adsorption has taken place,

(d) separating the discontinuous phase from the continuous phase, and

(e) dissociating the nucleic material, by desorption, from the particulate support by increasing the ionic strength up to an ionic strength greater than 10^{-2} M.

2. Process according to Claim 1, wherein for the desorption step (e), at least one of the parameters selected from the pH and the temperature is in addition varied as follows:

- increase in the pH up to a pH greater than 7,

- increase in the temperature up to a temperature greater than the LCST of the polymer.

3. Process for the isolation in aqueous phase of a nucleic material present in a sample by adsorption of said nucleic material onto a particulate support, comprising:

(a) providing an adsorption reagent comprising a sol consisting of an aqueous continuous phase and a discontinuous phase of the particulate support, which comprises a functionalized, particulate polymer, said polymer being obtained by polymerization of (1) a first water-soluble monomer of acrylamide or of an acrylamide derivative, (2) at least one cross-linking agent and (3) at least a second cationic and water-soluble functional monomer, said polymer having a predetermined lower critical solubility temperature (LCST) which is between 25 and 45°C,

(b) bringing into contact the adsorption reagent with the sample containing the nucleic material to absorb the nucleic material to the particulate support,

wherein, in said contacting step (b), the reaction medium has:

- an ionic strength at most equal to 10-2 M,

- a pH at most equal to 7, and

- a temperature less than the LCST of the polymer,

(c) optionally observing that the adsorption has taken place, and

(d) separating the discontinuous phase from the continuous phase.

5. Process according to Claim 1, wherein the particulate support consists of a functionalized particulate polymer obtained by polymerization of (1) a first water-soluble monomer of acrylamide or of an acrylamide derivative, (2) at least one water-soluble cross-linking agent and (3) at least a second cationic and water-soluble functional monomer, said

polymer having a predetermined lower critical solubility temperature (LCST) which is between 25 and 45°C.

6. Process according to Claim 1, wherein the particulate support comprises, in addition, an organic or inorganic core, completely or partially coated with said particulate polymer, said core not modifying the adsorption properties of the polymer in relation to said nucleic material.

7. Process according to Claim 6, wherein the core is a polystyrene core.

8. Process according to Claim 6, wherein the core comprises a magnetic compound.

9. Process according to Claim 1, wherein at least one probe and/or primer capable of specifically hybridizing to the nucleic material is added to the sample before contacting the adsorption reagent and the sample, or to the reaction medium after contacting the adsorption reagent and the sample.

10. Process according to Claim 1, wherein:

in the contacting step (b), the adsorption reagent is brought into contact with the nucleic material, the nucleic material consisting of a primer, in order to obtain a hybridization reagent, and

after having optionally observed that the adsorption has taken place, and separated the hybridization reagent from the reaction medium, said hybridization reagent is brought into contact with a medium containing at least one nucleic acid or nucleic acid fragment, under suitable conditions for the hybridization or the extension of the primer.

11. Process according to Claim 1, wherein the LCST of the polymer is between 30 and 40°C.

12. Process according to Claim 1, wherein the first monomer (1) is selected from N-alkylacrylamides and N,N-dialkylacrylamides.

13. Process according to Claim 12, wherein the first monomer (1) is selected from the group consisting of N-isopropylacrylamide, N-ethylmethacrylamide, N-n-propylacrylamide, N-n-propylmethacrylamide, N-isopropylmethacrylamide, N-cyclopropylacrylamide, N,N-diethylacrylamide, N-methyl-N-isopropylacrylamide, and N-methyl-N-n-propylacrylamide.

14. Process according to Claim 1, wherein the second functional monomer(s) (3) are selected from the group consisting of acrylic and methacrylic derivatives, 2-aminoethylmethacrylate chloride (AEM), the N-vinylpyridine derivatives, trialkylammonium derivatives and isothiouronium chloride derivatives.

15. Process according to Claim 1, wherein the cross-linking agent (2) is N,N-methylenebisacrylamide (MBA) or ethylene glycol dimethacrylate.

16. Process according to Claim 1, wherein the polymer is obtained in the presence of a polymerization initiator selected from water-soluble neutral and cationic initiators.

17. Process according to Claim 3, wherein it comprises, after the separation step (d), a desorption step according to which the nucleic material is dissociated, by desorption, from the particulate support by varying at least one of the parameters selected from the group consisting of ionic strength, pH and temperature, as follows:

- increase in the ionic strength up to an ionic strength greater than 10^{-2}M,
- increase in the pH up to a pH greater than 7,
- increase in the temperature up to a temperature greater than the LCST of the polymer.

18. Process according to Claim 1, wherein the separation step (d) is performed by a technique selected from the group consisting of centrifugation, filtration, precipitation, sedimentation, and the application of a magnetic field.

19. Process according to claim 13, wherein the first monomer is N-isopropylacrylamide (NIPAM).

20. Process according to claim 16, wherein the polymerization initiator is 2,2[1]-azobisamidinopropane chloride (V50).

21. Process according to Claim 1, wherein, for the desorption step (e), the temperature is in addition varied to a temperature greater than the LCST of the polymer.

22. Process according to Claim 17, wherein, for the desorption step, the temperature is varied to a temperature greater than the LCST of the polymer.

23. Process according to Claim 5, wherein the LCST of the polymer is between 30 and 40°C.